## REMARKS

The invention relates to a method for predicting a prognosis in a patient with severe immune response syndrome, a syndrome that includes sepsis, severe sepsis and septic shock. The method involves testing a body fluid from the patient for the presence or amount of one or more markers selected from amongst BNP, proBNP, and NT-proBNP.

Claims 1-6, 8-23, and 96-108 are pending in the application. Claims 1-4, 8, and 19 are currently under examination, with the remaining claims having been withdrawn from consideration by the Examiner as being drawn to a non-elected invention.

The specification has been amended herein to refer to Figures 5A through 5E and 6A through 6E. The subscripts "A" through "E" to which the Examiner refers represent different pages of multipage Figures 5 and 6. No new matter is added by this amendment.

Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

1. Restriction

Applicants affirm the election of MPIF-1 and TNFR1 made in response to the Examiner's telephonic request for a response to further restriction of the claims.

Applicants, however, traverse the restriction in accordance with MPEP § 818.03(d) to the extent the Examiner believes examination of claim 1 should be limited to the combination of MPIF-1 and TNFR1.

Applicants note that claim 1, which refers to a method of diagnosing sepsis comprising determining a concentration of at least one analyte in a test sample from said human subject; and further provides that at least one analyte is myeloid progenitor inhibitory factor-1 ("MPIF-1"), is a linking claim; that is, a genus claim linking all other claims pending in the application. All of the limitations of claim 1 are met by a method in which only a concentration of MPIF-1 is measured and used in the claimed method. This generic claim requires no material element to be added to that recited in the claim, and each of the remaining claims depends from this claim, and so require all of the limitations of claim 1. *See*, MPEP § 806.04(d) for the definition of a generic claim.

An applicant has a right to define what he regards as his invention as he chooses, so long as his definition is reasonably distinct, as required by 35 U.S.C. 112, second paragraph, and supported by an enabling disclosure, as required by the first paragraph of 35 U.S.C. 112. *Ex Parte Ohsumi*, 21 U.S.P.Q.2d 1020 (Appeal No. 90-2272, Bd. Pat. App. Interf. 1991). As noted in MPEP § 809, should claim 1 be allowable, the restriction between the linked inventions must be withdrawn, and the previously withdrawn claims must be rejoined and fully examined for patentability.

2. Drawings

The Examiner has objected to the drawings because the description did not reference Figures 5A through 5E and 6A through 6E. The subscripts "A" through "E" to which the Examiner refers represent different pages of multipage figures 5 and 6. Applicants respectfully submit that the foregoing amendments to the specification render moot the objection to the drawings.

3. Claims

The Examiner has objected to the claims, stating that claims 1-4 and 19 are drawn, in part, to non-elected subject matter. Applicants respectfully disagree.

As discussed in some detail above with regard to the Examiner's restriction of the claims, claim 1 refers to a method of diagnosing sepsis comprising determining a concentration of at least one analyte in a test sample from said human subject, and further provides that at least one analyte is myeloid progenitor inhibitory factor-1 ("MPIF-1"). As such, all of the limitations of claim 1 are met by a method in which only a concentration of MPIF-1 is measured. This generic claim requires no material element to be added, and each of the remaining claims depends from this claim, and so require all of the limitations of claim 1. Applicants request withdrawal of the objection.

4. Rejection of claims 1-4, 8, and 19 under 35 U.S.C. § 112, first paragraph (enablement)

Applicants respectfully traverse the rejection of claims 1-4, 8, and 19 as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

Applicants note that the Examiner has not examined the claims as they are written. The Examiner contends that "[t]he instant claims are drawn to methods of diagnosing sepsis in a human subject, comprising determining the concentration of myeloid progenitor inhibitory

factor-1 (MPIF-1) and tumor necrosis factor receptor-1 in a sample." Office Action, page 6. This is incorrect. As discussed above, all of the limitations of claim 1 are met by a method in which only a concentration of MPIF-1 is measured. It is improper for the Office to refuse to examine that which Applicants regard as the invention in this manner.

Applicants also note that the Examiner has taken issue with the definition of sepsis provided in the specification, asserting that "this definition encompasses many conditions and diseases that are not considered sepsis by the art. This includes diseases such as influenza, roseola, as well as conditions associated with trauma and surgery." Office Action, page 6. Such an assertion, however, is inconsistent with the definition of sepsis in the art.

The Examiner is directed to the consensus definition of sepsis published in Bone et al., *Chest* 101;1644-1655, 1992, Table 1:

> Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature >38ºC or <36ºC; (2) heart rate >90 beats per minute; (3) respiratory rate >20 breaths per minute or PaCO, <32 mm Hg; and white blood cell count >12,00Wcu mm, <4,000/cu mm, or >10% immature (band) forms.

Contrary to the Examiner's assertion, the definition of sepsis in the art is fully consistent with the definition in the present specification at paragraph [0002]. Infections such as influenza and roseola plainly can be within the definition of sepsis. Conditions associated with trauma and surgery may not be to the extent they are not (in the words of the specification) "infection-induced."

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *See, e.g.*, MPEP § 2164.01. A considerable amount of experimentation is permitted, provided that it is merely routine, or provided that the specification includes a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The factors relevant to an enablement analysis are enumerated in *In re Wands*, each of which is discussed below.

A. The nature of the invention

The present invention is related to the use of biomarker measurements for diagnosing sepsis. The specification specifically states that MPIF-1 may be used individually or together with other biomarkers in marker panels to provide a prognostic panel for diagnosis of sepsis.

B. The state of the prior art

Certain biomarkers have been used by artisans for diagnosis of sepsis. For example, the Examiner refers to publications concerning C-reactive protein ("CRP") and TNFR1 as diagnostic indicators in sepsis. Similarly, U.S. Patent 7,235,368 discloses the use of calcineurin B homologous protein as a sepsis diagnostic; and U.S. Patent 5,639,617 discloses the use of procalcitonin as a sepsis diagnostic. Thus, the skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis of patients and, as discussed above, has applied this established knowledge concerning biomarkers to sepsis.

As discussed above, the Examiner's assertion concerning the definition of sepsis is inconsistent with the prior art. Similarly, the Examiner has taken issue with the fact that MPIF-1 and TNFR1 might be elevated in conditions other than sepsis, asserting that this makes these markers "unacceptable for the diagnosis of sepsis." Office Action, page 8. It is not clear on what scientific basis the Examiner is basing this assertion, as no scientific reasoning or reference is provided in support. If this is the Examiner's personal opinion it is respectfully that the Examiner explicitly assert that this is the Examiner's personal opinion.

Virtually all diagnostic tests lack the type of specificity the Examiner implies is necessary. While one might desire to have available "specific markers" for a particular disease or condition, that is not necessary for one to practice the claimed methods without undue experimentation and with a reasonable level of predictability. Fortunately, even nonspecific markers can be useful clinically when in the hands of the skilled artisan, as the skilled artisan does not use such tests in an informational vacuum. Rather, diagnostic tests are used by skilled medical personnel in concert with other available medical indicia related to a subject, and are not judged by the ability of a "specific marker" to give a definitive yes/no answer to the existence of a disease.

For example, procalcitonin is not a "specific marker" of sepsis, but instead is elevated in "various non-infectious conditions." FDA 510-k summary K040887, page 7 (approving procalcitonin as a sepsis diagnostic). Nevertheless, it is an FDA-approved test for use in the

evaluation of sepsis, and so presumably is "acceptable for the diagnosis of sepsis," in sharp contrast to the grounds asserted under the enablement rejection. The same is true of many markers in many disease states. Thus, D-dimer is not a "specific marker" of pulmonary embolism. *See, e.g.*, Indik and Alpert, *Prog. Cardiovasc. Dis.* 42: 261-272, 2000, page 262 ("Since D-dimer products are produced whenever there is active intravascular thrombosis and fibrinolysis in the body, the specificity of all DD assays is expected to be low"). Nevertheless, it is an FDA-approved test for use in the evaluation of pulmonary embolism. Assays that detect B-type natriuretic peptide are FDA-approved for use in the diagnosis of heart failure. But, BNP is also FDA-approved as a risk marker in acute coronary syndromes. *See, e.g.*, Triage® BNP Test package insert, page 1, section entitled "Intended Use." Elevated levels in the well known "prostate-specific antigen" ("PSA") test may be caused by conditions including prostate cancer, benign prostate enlargement, inflammation, and infection, and elevations are understood to be affected by both age and race. *See, e.g.*, http://www.nlm.nih.gov/medlineplus/ency/article/003346.htm. Nevertheless, the PSA test is routinely used by artisans for initial diagnosis and screening. And CRP is a marker that is elevated in numerous inflammatory processes, including cancer, connective tissue disease, heart attack, infection, inflammatory bowel disease, lupus, pneumococcal pneumonia, rheumatoid arthritis, rheumatic fever, and tuberculosis. *See, e.g.*, http://www.nlm.nih.gov/medlineplus/ency/article/003356.htm. While only a fraction of subjects having an increased CRP level will have any one of these conditions, CRP tests are FDA approved and routinely used by clinicians. In sum, as indicated by the foregoing examples, there is ample evidence directly refuting the assertion that a marker(s) has to be specific to a single condition or disease. Put another way, the fact that MPIF-1 and TNFR1 might be elevated in conditions other than sepsis does render the claimed markers as unacceptable in diagnosis of sepsis.

C. The relative level of skill in the art

The skilled artisan has extensive experience with the clinical use of biomarker tests for diagnosis of patients and, as discussed above, has applied this established knowledge concerning biomarkers for diagnosis of sepsis. The skilled artisan is prepared to perform the required studies to establish these performance characteristics for the particular patient population seen at each

institution, and understands that the required analyses such as immunoassay methods and ROC analysis are necessary and routine, even in the use of the most well-established biomarkers.

D. The quantity of experimentation necessary

The present specification demonstrates that MPIF-1, and several other markers including TNFR1, are significantly elevated in patients with sepsis. This elevation was seen relative to normal subjects, and "mimic" subjects that had illness severe enough to warrant hospital admission but did not have sepsis. *See, e.g.*, specification, paragraphs [0086] and [0196], and Table 7.

Once suitable biomarker(s) have been identified, the remaining experimentation is precisely that performed routinely in the art. For example, an assay, often an immunoassay, is developed for the polypeptide of interest using methods well known in the art. The biomarker(s) are measured in samples obtained from individuals in two populations, generally a "diseased" population (*e.g.*, one that has suffered from a particular outcome) and a "normal" population (*e.g.*, one that has not suffered from that outcome). If desired, a "cutoff" value for a particular marker that provides a desired sensitivity and specificity may be determined using standard analysis methods, such as ROC analysis.

On page 8 of the Office Action, the Examiner seems to imply that a marker must be 100% sensitive (that is, positive in all sepsis patients) in order to meet the enablement requirement: "the fact that severe sepsis was required for TNF-R1 levels to be significantly raised further highlights the fact that increased TNF-R1 levels are unacceptable for the diagnosis of sepsis." Artisans, however, understand that, just as diagnostic tests are not generally 100% sensitive, diagnostic tests are not generally 100% specific. Nevertheless, such tests are viewed in the art as being useful diagnostics.

Consider, for example, procalcitonin, which is the subject of U.S. patent 5,639,617 for the diagnosis of sepsis. As demonstrated in the graph on page 6 of the FDA 510-k summary K040887, subjects with sepsis largely overlap with non-infected controls, and it is not until sepsis becomes more severe that the test generates a high risk of sepsis. Nevertheless, the FDA has approved this test and, as demonstrated on page 5 of K040887, artisans consider this test to be a reliable sepsis diagnostic. Whether or not such a marker such as procalcitonin or TNFR1 may be more effective in the case of more severe disease, such markers are used by those of skill

in the art for diagnosing sepsis, notwithstanding that it may not be able to identify 100% of sepsis patients.

E. The predictability of the art

In the present case, the methods to be followed are all routine; the only issue that remains is an identification of which markers to apply to sepsis diagnosis, an issue that is solved by reference to the present specification and claims.

F. The amount of direction or guidance

As noted, the methods to be followed are all routine; the only issue that remains is an identification of which markers to apply to sepsis diagnosis. Guidance on that point is provided by the specification.

F. The presence or absence of working examples

The present application provides exemplary data for numerous markers of sepsis. Included among these examples are MPIF-1 and TNFR1. *See, e.g.*, Specification, Table 7.

H. The breadth of the claims

The claims refer to the use of MPIF-1, individually or in panels for, diagnosis of sepsis, and are thus circumscribed in their breadth. As discussed herein, comments in the Office Action, *e.g.*, concerning the breadth of the definition of sepsis, suggest a lack of understanding of the knowledge available in the art.

I. Conclusion

It is well established in the patent law that a specification is presumed to be enabling. Also, as stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In the present case, the skilled artisan can, by simply following the extensive detailed guidance in the specification, perform the claimed methods. Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

## CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

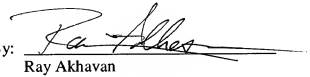
Please direct all correspondence to the undersigned attorney or agent at the address indicated below.

## FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415** (Docket No 10759216).

Respectfully submitted,

Date: February 22, 2008

By: 

Ray Akhavan
Registration No. 58120

**WILSON SONSINI GOODRICH & ROSATI**
650 Page Mill Road
Palo Alto, CA 94304-1050
Direct Dial: (202) 973-8832
**Customer No. 21971**